Formal Desymmetrization of the Diastereotopic Chains in Gemini Calcitriol Derivatives with Two Different Side Chains at C-20[‡]

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Keywords: Alkylation / Hydroboration / Diastereoselectivity / Ene reaction

Derivatives of calcitriol with two equal side chains emanating at C-20, also known as gemini, have emerged as interesting compounds, either as instruments for assessing the steric requirements of the vitamin D receptor or as drug candidates. We now describe the syntheses of gemini analogs where the two side chains differ from each other. While retaining the 2-hydroxy-2-methylpentyl moiety, common to both calcitriol and gemini, as one chain, we replaced the other with a 1,1,1-trifluoro-2-hydroxy-2-(trifluoromethyl)-3-pentynyl group. The features comprising this chain modification are commonly regarded to improve toxicity profiles and drug performance. The resulting epimeric pairs with a new stereogenic center at C-20 were resolved and the absolute configurations assigned. The side-chain desymmetrization protocols described herein serve as a basis for additional synthesis activity in this area.

Introduction

The transcription-factor activity of calcitriol is mediated by the vitamin D receptor (VDR), heterodimerization with the retinoid X receptor (RXR), coactivator proteins and specific DNA binding sites.[1−3] It has been recognized that the change in calcitriol (**1**) to the (*S*)-configuration at C-20,[4] as in **2**, can substantially and positively influence the gene-transcription activity. This change was attributed to the increased affinity of **2** for the VDR. Agonist-induced conformational changes in the VDR were postulated to be the basis of the molecular switch in nuclear calcitriol signaling.[5−7] More recently, however, it was shown that the interaction between the 20-epi agonist **2** and the VDR does not significantly alter the conformation of the ligand-binding domain from the one that accommodates the natural ligand **1**. Accordingly, the ligand conformation is assumed to adapt to the binding pockets of the relatively invariant binding domain and structural variations of the ligands are subject to the constraints dictated by the pockets.[8]

From the vantage point of the chemist, this theory is very appealing as it would permit the modeling, synthesis and evaluation of compounds that must fulfil chemical criteria in accordance with a more or less rigid ligand-binding domain conformation. Indeed, the studies that compared **1** with its C-20 epimer **2**, and demonstrated large differences in their antiproliferative activities in several cell types in favor of **2**, do not dispute this hypothesis, since very similar ligand-binding domain conformations have been demonstrated for both agonists.[8] In view of the observation that either of the C-20 epimers is being accommodated in the ligand-binding domain, it becomes of interest to replace the C-20 methyl group of calcitriol and 19-nor-calcitriol with a second side chain. The resulting derivatives **3** and **4**, now featuring two identical side chains and commonly referred to as gemini and 19-nor-gemini, respectively, have very recently been studied by Moras.[9] In spite of the drastic increase of the molecular volume caused by the second chain, he has shown that this chain does not push for additional space; one of the chains assumes the ''natural'' position in the ''designated'' pocket for the calcitriol side chain, while the other one is accommodated by an ''induced fit''. Clearly, gemini, as a new type of agonist, would not have been suggested as a chemical structure based on molecular modeling but was conceived as a tool to survey the ligand-binding domain by first producing the substance and to investigate the binding ability afterwards. Precisely the same concept governs the present account. We are now interested in the synthesis and subsequent evaluation of gemini analogs containing two *different* side chains. The stereocenter at C-20, common to the natural hormone **1** and its epi-analog, **2**, has been restored in these molecules thus providing pairs of epimers that are uniquely qualified for the exploration of the stereochemical requirements at the ligand-binding domain.

In the calcitriol series of compounds it was demonstrated that a modification of the side chain featuring a geminal

[‡] Calcitriol Derivatives with Two Different Side Chains at C-20, Part I.

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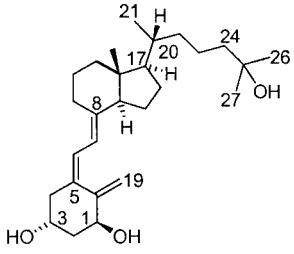
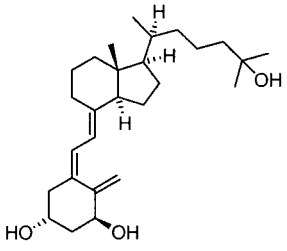
trifluoromethyl arrangement at C-25 and a triple bond between C-23 and C-24 enhances the anti-proliferative activity of the substrate.[10,11] Thus, maintaining the constitution of the calcitriol side chain for one, and providing the other with the above-mentioned modifications, was our first choice for synthesis. Two scenarios could be envisioned in subsequent docking experiments with the VDR. A given stereoisomer may place the "natural" chain in the designated pocket but, due to increased size and rigidity, the VDR may have difficulty in efficiently accommodating the other. Alternatively, then, the modified and more rigid chain may occupy the pocket designated for the "natural" chain so that the "natural" chain can be accommodated by the "induced fit". Preliminary studies already suggest considerable differences between the C-20 epimers in their regulatory activity of cellular proliferation and differentiation, suggesting discrimination in agonist acceptance by the VDR.[12]

The therapeutic potential of the dual side chain modification was shown to compare favorably with calcitriol (**1**), whose inhibition of proliferation and induction of differentiation of various malignant cells is well established. In that study, **3** was a much more potent clonal growth inhibitor of a number of cancer cells.[2] That the CD-ring assembly constitutes an essential element for agonist activity was demonstrated by the synthesis and evaluation of **5**, which is devoid of this spacer and lacks biological activity even at the highest concentrations.[1] The two side chains in **5** obviously did not compensate for the required anchoring points along the axis spanning the 1,3,25-trihydroxy configuration of the conventional agonists.[8]

In the present account we describe compounds featuring the basic architecture of **3** and **4** described previously[13–15] but limit the change to one of the side-chain constructs. Subsequent investigations will guide us in the determination of the optimum configuration required not only for accom-



1



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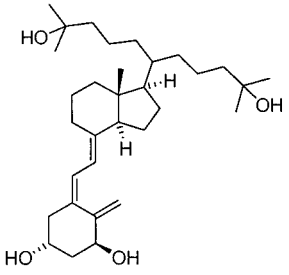

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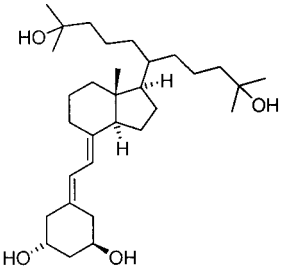

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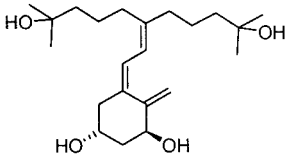

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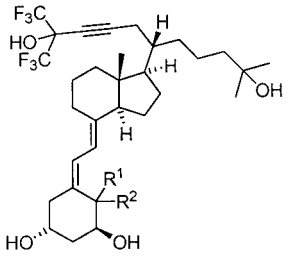
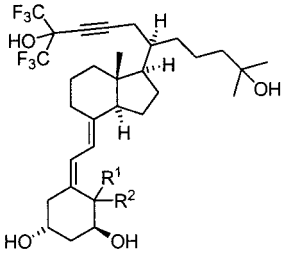


6a: $R^1 + R^2 = CH_2$
6b: $R^1 = R^2 = H$

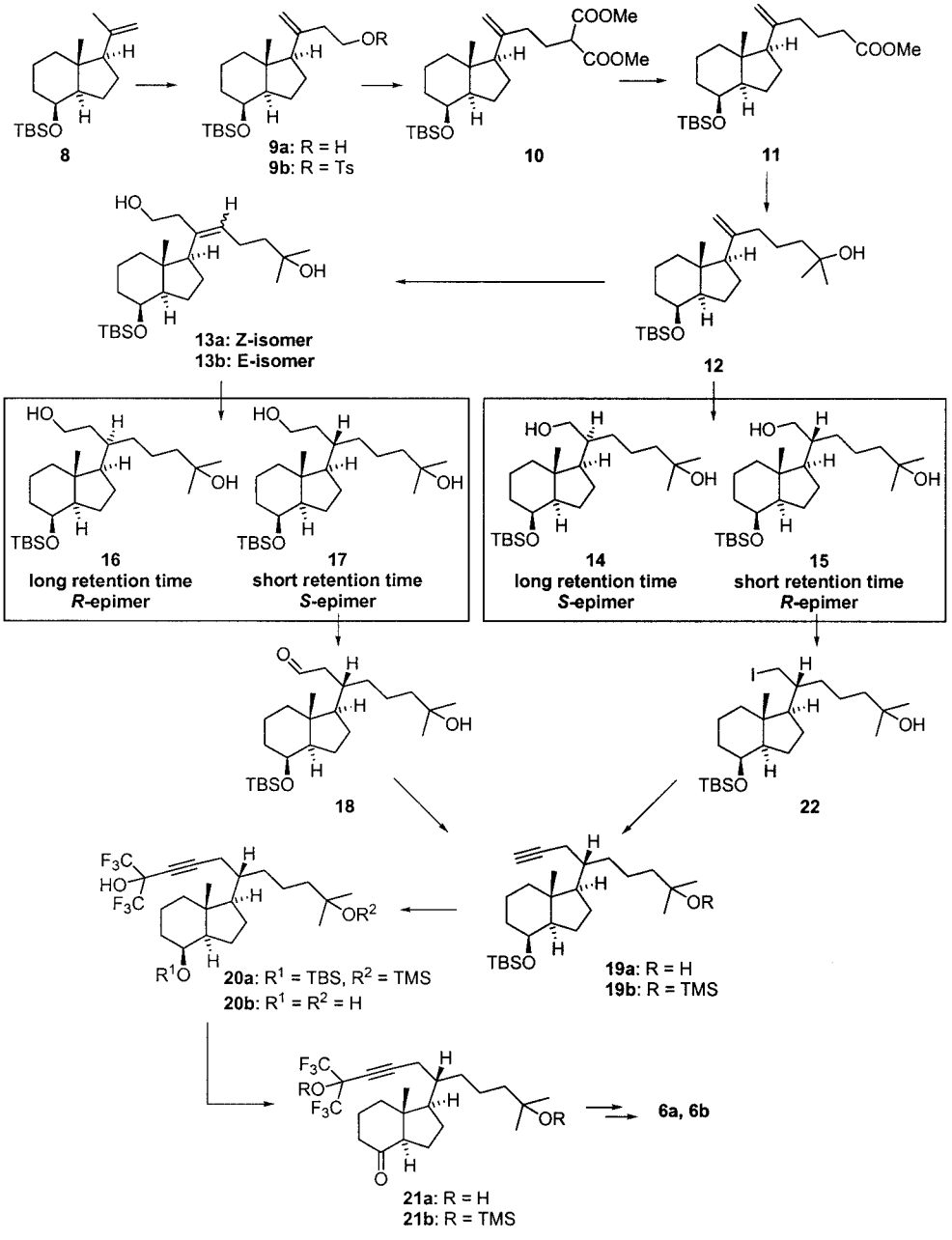


7a: $R^1 + R^2 = CH_2$
7b: $R^1 = R^2 = H$

modation in the VDR but also for the maximum expression of biological activity. Preliminary studies of compounds **6** and **7** revealed these activities to include inhibition of renin biosynthesis[16] and cancer cell growth.[17]

Results and Discussion

The stereo-defined construction of the two different side chains at C-20, tantamount to desymmetrization of the gemini side-chains, required a path that would not only lead to both epimers but also, hopefully, to the stereospecific synthesis of a particular epimer once a preferred configuration at C-20 had been established and process development was indicated. We therefore planned to select a CD-ring assembly containing one completed side chain and a strategically placed section with a diastereotopic face that could be subject to hydrogen transfer from an achiral reducing agent to produce both suitably functionalized epimers in one step. In the course of further drug development, hydrogen transfer from a chiral reducing agent could later be exploited for a stereoselective production of the drug substance. Alkenol **12** (Scheme 1) emerged as an ideal desymmetrization platform as it contains the preformed side chain of vitamin D_3 and an alkene moiety disposed to function as the diastereotopic hydrogen acceptor. More specifically, conventional hydroboration of **12** would lead to an epimeric pair of diols **14** and **15**, suitable for further elaboration of



Scheme 1

the second side chain. Alternatively, **12** could be subjected to an ene reaction with formaldehyde to lead to an alkenediol **13** wherein hydrogen transfer from the achiral reducing agent to the newly formed diastereotopic face would provide the epimeric pair of diols **16** and **17** that are also suitable for further side-chain elaboration.

In pursuit of this plan, the key intermediate **12** was constructed, as shown in Scheme 1, by an ene reaction with formaldehyde using the alkene **8** [6,13−15,18] as substrate. The resulting alcohol **9a** was *O*-tosylated and the tosyloxy group in **9b** displaced with dimethyl sodiomalonate leading to the diester **10**. A demethoxycarbonylation[19] led to the monoester **11** and subsequent treatment with methylmagnesium bromide gave the required alkenol **12**. Hydroboration of this material provided **14** and **15** as a mixture in a ratio of 2:3 that was easily separated by preparative HPLC.

Conducting a second ene reaction with formaldehyde converted **12** into **13** as a mixture of (*E*) and (*Z*) isomers, the latter isomer, however, only as a minor component. Although the mixture was readily separated by flash chromatography, the presence of two isomers was deemed immaterial for the task at hand so that the ene product was used directly in the next step. While hydrogenation of **13** with Pd−C caused extensive hydrogenolysis of the homoallylic alkenol, Pt−C gave a clean conversion into the desired diols **16** and **17** in nearly equal proportions. This epimeric pair could again be separated quantitatively by chromatography so that both epimers were now available for further advancement. The absolute configuration of the side-chain stereocenter in each epimer, generated either by hydroboration (**14**/**15**) or hydrogenation (**16**/**17**), was not obvious for some time, however.

The diol **17**, exhibiting the shorter retention time on the HPLC column, was oxidized to the aldehyde **18** with pyridinium chlorochromate and immediately converted with (1-diazo-2-oxopropyl)phosphonic acid dimethyl ester[20,21] to the acetylene **19a** as shown in Scheme 1, then treated with 1-(trimethylsilyl)imidazole to afford the disilyl ether **19b**. Addition of hexafluoroacetone furnished the side chain construct as depicted in **20a** and in the target compounds **6a** and **6b**. The two silyl ether protective groups in **20a** were cleaved simultaneously with aqueous fluorosilicic acid[22,23] in acetonitrile to give the corresponding triol **20b**. Subsequent oxidation with pyridinium dichromate furnished ketone **21a**. This compound was obtained in crystalline form suitable for crystallographic analysis whose result is illustrated in Figure 1. Although the absolute configuration was not determined in this study, the *threo* configuration of the bond connecting the indenone ring with the side chain assembly was immediately obvious and thus established the (6*S*)-configuration [corresponding to (20*S*) in the steroid nomenclature].

Similarly, **26a**, the epimer of **21a**, was obtained starting with the diol **16** followed by subsequent conversions to aldehyde **23**, acetylenes **24a**, **24b**, **25a** and triol **25b**, as described for the synthesis of **21a** and illustrated in Scheme 2.

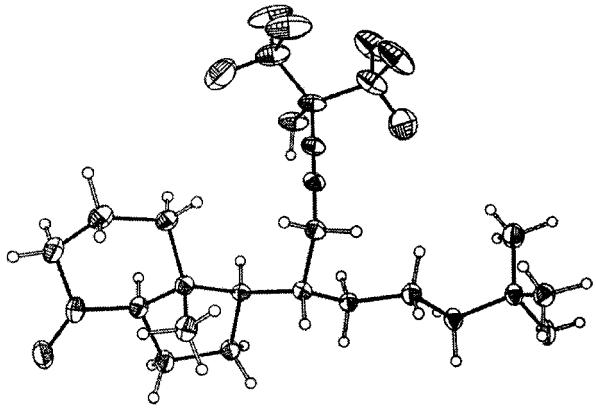
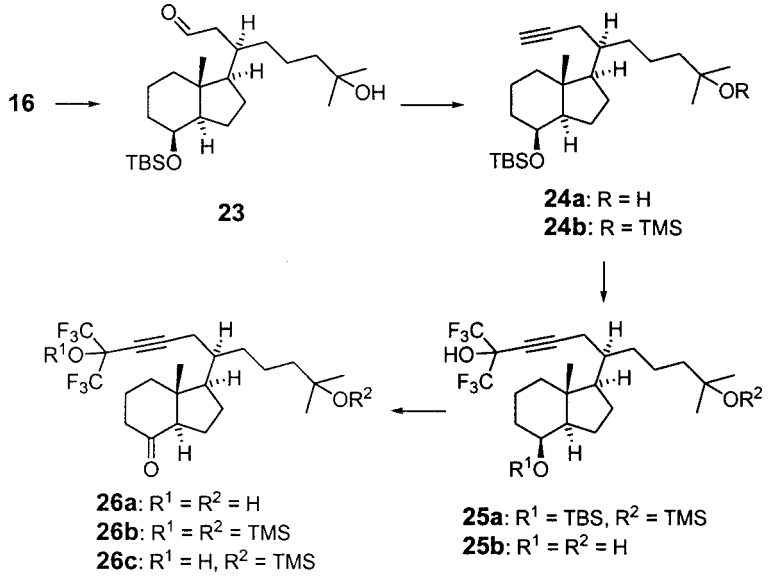


Figure 1. A molecule of **21a** in the crystal

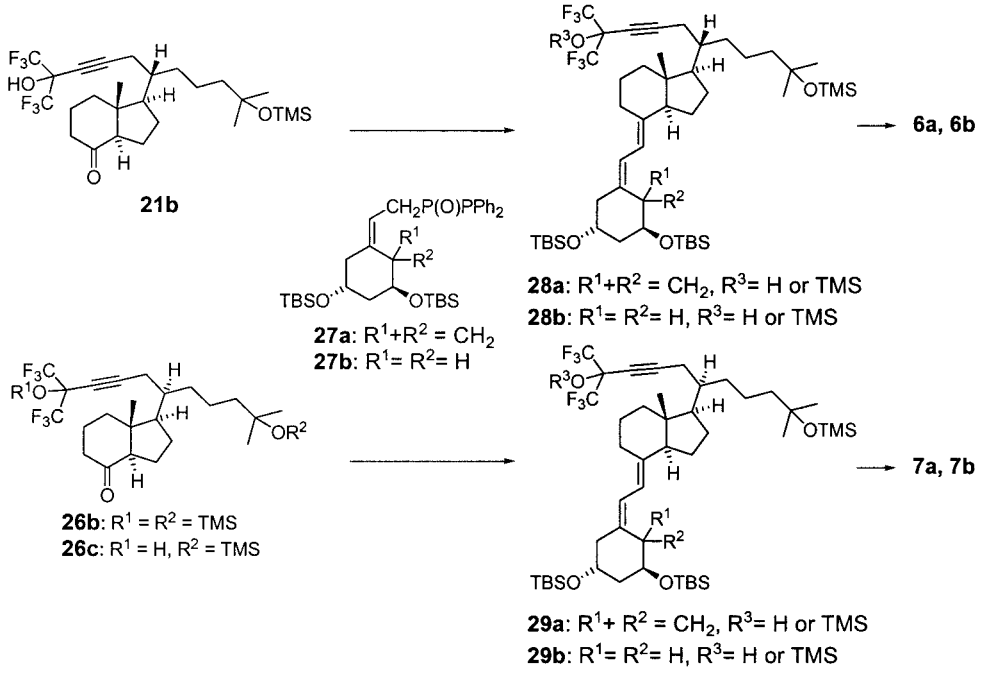


Scheme 2

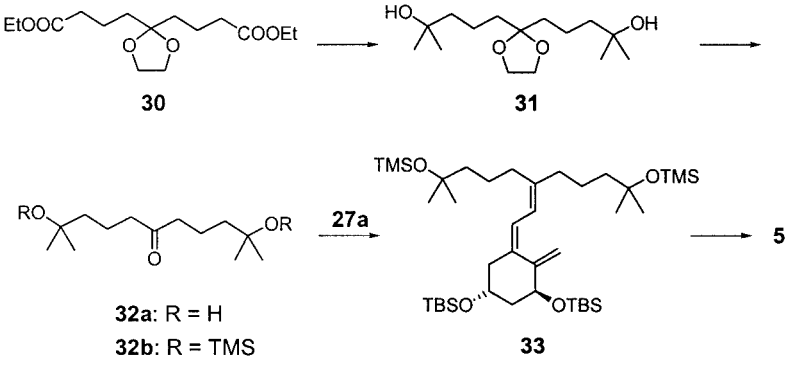
To correlate the absolute configurations of the pair of epimers derived from the hydroboration experiment with those established for **16** and **17**, it became essential to synthesize one of the members that is part of the sequence that extends from the diol **17** to ketone **21**, or from diol **16** to ketone **26**, but starting with one of the hydroboration products **14** or **15** and to assess its stereochemical identity by comparison. This task was simplified as the ^{1}H NMR spectra of the intermediates **17** to **21** are quite different than their counterparts in the other epimeric series extending from **16** to **26**. We selected diol **15**, the component that exhibits the shorter retention time on the HPLC column, and converted it into the iodo compound **22** as shown in Scheme 1. Treatment of this material with lithium acetylide DMA complex in DMF gave mostly the elimination product **12**, but a sufficient quantity of the acetylene was produced to permit a stereochemical assignment. It could be shown that the acetylene produced in this fashion was identical with **19a**, and rather different from the epimeric **24a**. Consequently, the stereochemical assignments for both epimeric pairs **14**/**15** and **16**/**17** was now solved; **15** and **17**, the diols with the shorter retention time on the HPLC column, are established as the (*R*)- and (*S*)-epimers, respectively, as summarized in Scheme 1.

While ketone **21a** gave the disilyl ether **21b** upon treatment with 1-(trimethylsilyl)imidazole, ketone **26a** produced a mixture of silyl ethers **26b** and **26c** under similar reaction conditions (Scheme 2). The standard coupling protocol,[24] employing the allyldiphenylphosphane oxides **27a** and **27b** as Wittig−Horner components,[25−27] gave the two pairs of poly-*O*-silylated intermediates **28a**/**28b** and **29a**/**29b**, and a single treatment with tetrabutylammonium fluoride liberated all protected hydroxy groups present in each species to furnished the final compounds **6a, 6b**, **7a** and **7b** as shown in Scheme 3.

The selection of the two pairs **6a**/**6b** and **7a**/**7b** for exploring stereochemical effects in the VDR gained in validity when it could be shown that the environment experienced by a particular side chain of one epimer is quite different from that of the other, as suggested by their ^{1}H NMR spec-



Scheme 3



Scheme 4

tra. Similarly, the ^{19}F NMR spectra show the geminal trifluoromethyl groups in one pair in a different chemical environment to the other. More specifically, the representatives with the (20*S*)-configuration, as in **6a** and **6b**, exhibit the geminal trifluoromethyl groups as overlapping quadruplets, while the (20*R*)-pair **7a/7b** show the same signals as singlets.

The ketone **32b**, required for the synthesis of **5**, was prepared from diethyl 1,3-dioxolane-2,2-dibutyrate[28] **30** by a sequence of reactions commencing with a treatment with methylmagnesium bromide solution (Scheme 4). The resulting dioxolane **31** was hydrolyzed to give the ketone **32a** that was used directly in the next step as chromatographic purification gave variable recoveries, probably due to hemiacetal formation. Thus, crude **32a** was converted into **32b** with 1-(trimethylsilyl)imidazole, then further condensed with **27a** to afford **33**, which, after deprotection, gave the tetraol **5**. To investigate the effect on product yield, we conducted the condensation deliberately without the usual excess of the A-ring component and observed a value of 51%.

The pharmacological evaluation of compounds **6a**, **6b**, **7a** and **7b** is presently ongoing.

Experimental Section

All operations involving vitamin D analogs were conducted in amber-colored glassware under nitrogen. Tetrahydrofuran was distilled from sodium benzophenone ketyl just prior to use and solutions of solutes were dried with sodium sulfate. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were measured at 25 °C. ^1H NMR spectra were recorded at 400 MHz with $CDCl_3$ as solvent unless indicated otherwise. TLC was carried out on silica gel plates (Merck G-60, F254) with visualization under short-wavelength UV light or by spraying the plates with 10% phosphomolybdic acid in methanol followed by heating. Flash chromatography[29] was carried out on 40−65 μm mesh silica gel. Final products are amorphous solids and obtained by evaporation of methyl formate solutions. Preparative HPLC was performed on a 5 × 50 cm YMC column using 15−30 μm mesh silica gel at a flow rate of 100 mL/min.

3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]but-3-enyl Tolene-4-sulfonate (9b): Tosyl chloride (5.91 g, 31 mmol) was added in one portion to a stirred solution containing the alcohol **9a** (6.59 g, 19.5 mmol), dichloromethane (53 mL), triethylamine (6.0 mL, 43 mmol) and DMAP (244 mg, 2.0 mmol). After 5 h the resulting suspension was poured into a mixture of ice (50 g), saturated sodium hydrogen carbonate solution (100 mL) and hexane (100 mL). The aqueous layer was re-extracted with dichloromethane (40 mL). These combined extracts were washed with 1:1 water-saturated sodium hydrogen carbonate solution (122 mL), saturated sodium hydrogen carbonate solution (100 mL), then dried (sodium sulfate) and the solvents evaporated. The residue was purified on a short flash chromatography column using ethyl acetate/hexane (1:39) as mobile phase to yield **9b** as a colorless oil (9.51 g, 99%). ^1H NMR: δ = −0.007 and 0.005 (s, 3 H each), 0.73 (s, 3 H), 0.88 (s, 9 H), 1.05 (m, 1 H), 1.25−1.8 (m, 10 H), 1.88 (m, 1 H), 2.28 and 2.39 (m, 1 H each), 2.45 (s, 3 H, Me), 3.99 (m, 1 H, C4-H), 4.09 (m, 2 H), 4.81 and 4.82 (s, 1 H each), 7.34 and 7.79 (d, J = 8.4 Hz, 2 H each) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = −5.17, −4.79, 14.71, 17.65, 17.97, 21.61, 22.66, 24.56, 25.76 (3C), 34.34, 36.20, 39.43, 42.78, 52.89, 56.64, 68.97, 69.01, 69.33, 112.72, 127.86 (2 C), 129.71 (2 C), 133.15, 143.30, 144.58 ppm. LR-FAB(+): m/z = 493 [M + H], 491 [M − H], 361 [M − OTBS]. HRMS-ES(+) calcd. for $C_{27}H_{44}O_4SSi$: 515.2628 [M + Na], found 515.2622.

Dimethyl 2-{3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]but-3-enyl}malonate (10): A solution of dimethyl malonate (17.17 g, 130 mmol) in toluene (50 mL) was added dropwise to a stirred suspension of sodium hydride (4.66 g, 117 mmol) in toluene (160 mL). The suspension was heated in a 120 °C oil bath for 5 min, then a solution of tosylate **9b** (9.50 g, 19.3 mmol) in toluene (100 mL) was added dropwise with vigorous stirring. Stirring in the 120 °C bath was continued for 5 h (TLC, ethyl acetate/hexane, 1:6). The flask was then placed into an ice bath and pieces of ice and water (100 mL) were added to dissolve the voluminous precipitate. The mixture was equilibrated with hexane (100 mL) and the resulting aqueous phase was re-extracted once with toluene (50 mL). The combined extracts were washed with water (100 mL) and brine (50 mL) then dried (sodium sulfate) and the solvents evaporated. The residual oil was concentrated to remove most of the dimethyl malonate. The resulting oil (10.8 g) was flash chromatographed with hexane, and ethyl acetate/hexane (1:79 and 1:39) as mobile phases to give pure **10** (6.75 g) as an oil. Re-chromatography of the side fractions gave an additional crop of **10** (1.19 g), total yield 91%. ^1H NMR: δ = 0.002 and 0.012 (s, 3 H each), 0.78 (s, 3 H), 0.88 (s, 9 H), 1.15 (m, 1 H), 1.3−1.8 (m, 11 H), 1.97−2.10 (m, 4 H), 3.38 (m, 1 H), 3.73 and 3.74 (s, 3 H each), 4.01 (m, 1 H), 4.82 and 4.89 (br. s, 1 H each) ppm. LR-FAB: m/z = 453 [M + H], 451 [M − H], 431 [M − OMe], 395 [M − C_4H_9], 321 [M − OTBS]. HRMS-ES(+) calcd. for $C_{25}H_{44}O_5Si$: 475.2850 [M + Na], found 475.2863.

Methyl 5-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]hex-5-enoate (11): A mixture of the diester **10** (8.27 g, 18.27 mmol), water /DMSO (1:100) (35 mL) and lithium chloride (1.71 g) was stirred and heated under nitrogen in a bath maintained at 160 °C for 3 h. Reaction progress was monitored by TLC (ethyl acetate/hexane, 1:9). The light-tan solution was cooled and was then distributed between water (100 mL) and hexane (200 mL). The aqueous layer was extracted with hexane (2 × 50 mL). The combined hexane layers were washed with water (2 × 50 mL), once with brine (20 mL) then dried (sodium sulfate) and the solvents evaporated to leave a tan oil that was flash chromatographed with a stepwise gradient of dichloromethane/hexane (1:39 and 1:19), then ethyl acetate/hexane (1:79) to give **11** as a colorless oil, 6.29 g, 87%. ^1H NMR: δ = 0.004 and 0.013 (s, 3 H each), 0.79 (s, 3 H), 0.89 (s, 9 H), 1.16 (m, 1 H), 1.3−1.8 (m, 12 H), 2.02 (m, 3 H), 2.30 (m, 2 H), 3.67 (s, 3 H, Me), 4.02 (m, 1 H), 4.80 and 4.88 (br. s, 1 H each) ppm. LR-APCI(+): m/z = 395 [M + H], 393 [M − H], 363 [M − OMe], 263 [M − OTBS]. HRMS-ES(+) calcd. for $C_{23}H_{42}O_3Si$: 395.2976 [M + H], found 395.2980.

6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2-methylhept-6-en-2-ol (12): A 3 M solution of methylmagnesium bromide in diethyl ether (15 mL) was added dropwise to an ice-cold solution of the ester **11** (5.60 g, 14.19 mmol) in diethyl ether (120 mL). After completion of the addition the mixture was stirred at room temperature for 3 h then cooled again in an ice bath. A saturated solution of ammonium chloride (25 mL) was added dropwise. The resulting precipitate was dissolved by the addition of water (80 mL). The aqueous layer was re-extracted with diethyl ether (100 mL) and the combined diethyl ether layers were washed with pH 7 phosphate buffer (30 mL), then dried (sodium sulfate) and the solvents evaporated to afford crude

12 as a colorless oil. This material was flash-chromatographed with ethyl acetate/hexane (1:39) as mobile phase until the product started to emerge from the column (TLC, ethyl acetate/hexane, 1:4, R_f = 0.49). For subsequent elution ethyl acetate/hexane (1:19) was used. Fractions representing pure product were pooled and the solvents evaporated to give **12** as a colorless oil (3.0 g). Fractions preceding the main band contained a small amount of a less-polar impurity (2.62 g). This material was re-chromatographed on an HPLC column (see Exp. Sect.) using ethyl acetate/hexane (1:20) as mobile phase. After ca. 4.5 L of effluent, fractions were taken to give additional pure **12** (1.95 g) as a colorless oil, 88%. ^{1}H NMR: δ = 0.005 and 0.013 (s, 3 H each), 0.79 (s, 3 H), 0.88 (s, 9 H), 1.17 (m, 1 H), 1.22 and 1.23 (s, 3 H each), 1.35−1.85 (m, 16 H), 2.01 (m, 2 H), 4.02 (m, 1 H, C4-H), 4.78 and 4.88 (br. s, 1 H each) ppm. LR-FAB(+): *m*/*z* = 395 [M + H], 377 [M − OH]. HRMS-ES(+) calcd. for $C_{24}H_{46}O_2Si$: 395.3340 [M + H], found 395.3344. $C_{25}H_{48}O_3Si$: calcd. C 73.03, H 11.75; found C 72.82, H 11.97.

(*Z*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]but-2-en-1-ol (13a) and (*E*)-3-[(1*R*,3a*R*,-4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]but-2-en-1-ol (13b): A 1.0 M solution of dimethylaluminum chloride in hexane (1.2 mL) was added to a stirred, cold (−20 °C) suspension of alkene **12** (231.6 mg, 0.587 mmol) and paraformaldehyde (21 mg, 0.70 mmol) in dichloromethane (2 mL). The cooling bath was replaced by an ice bath after 2 h and additional quantities of paraformaldehyde (16 mg, 0.53 mmol) and 1 M dimethylaluminum chloride solution (0.5 mL) were added. No starting material could be detected after 10 min (TLC, EtOAc). The resulting solution was stirred for an additional period of 10 min then poured onto crushed ice and acidified with 0.1 M hydrochloric acid. The mixture was extracted with diethyl ether (2 × 15 mL), the combined extracts were washed with brine (10 mL), dried (sodium sulfate), and the solvents evaporated to a colorless oil. This material was flash-chromatographed with ethyl acetate/hexane (1:3) as mobile phase. The minor component with R_f = 0.44 (4 mg) was identified as the (*Z*) isomer **13a**. ^{1}H NMR: δ = 0.005 and 0.014 (s, 3 H each, Me_2Si), 0.86 (s, 3 H), 0.88 (s, 9 H), 1.10 (m, 1 H), 1.21 and 1.22 (s, 3 H each), 1.32−1.45 (m, 3 H), 1.45−1.84 (m, 11 H), 2.05 (m, 1 H), 2.20 and 2.38 (m, 1 H each, hydroxymethyl CH_2), 2.27 (m, 1 H), 2.54, (t, *J* = 9.9 Hz, 1 H), 3.48 and 3.63 (m, 1 H each, hydroxymethyl), 4.04 (br. s, 1 H), 5.36 (dd, *J* = 5.5 Hz, 1 H) ppm. Irradiation of the alkene region δ = 5.35 ppm resulted in an NOE at δ = 2.20 ppm and vice versa, supporting the (*Z*) geometry. Compound **13a** preceded fractions containing mixtures of **13a** and **13b** (110 mg) and the main band with R_f = 0.30 representing the pure (*E*) isomer **13b** (80 mg). This residue was redissolved in hexane and crystallized. ^{1}H NMR: δ = 0.002 and 0.012 (s, 3 H each), 0.78 (s, 3 H), 0.88 (s, 9 H), 1.12 (m, 1 H), 1.24 (s, 6 H), 1.26−1.8 (m, 14 H), 2.03 (m, 1 H), 2.19 (m, 3 H, 1 H of hydroxymethyl CH_2), 2.54 (m, 1 H, 1 H of hydroxymethyl CH_2), 3.60 (m, 2 H, hydroxymethyl), 4.01 (br. s, 1 H), 5.37 (dd, *J* = 7, *J* = 7.3 Hz, 1 H) ppm. Irradiation of the angular methyl region at δ = 0.78 ppm resulted in an NOE at the alkene region δ = 5.37 ppm supporting the (*E*) geometry. $[\alpha]_D^{25}$ = +30.38 (*c* = 0.43, methanol). LR-FAB(+): *m*/*z* = 425 [M + H], 423 [M − H], 407 [M − OH], 351 [M − HOCMe_2CH_2]. $C_{25}H_{48}O_3Si$: calcd. C 70.70, H 11.39; found C 70.74, H 11.38.

(*R*)-2-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-6-methylheptane-1,6-diol (15) and (*S*)-2-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-6-methylheptane-1,6-diol (14): A solution of the alkenol **12** (2.5 g, 6.33 mmol) in tetrahydrofuran (9 mL) was cooled in an ice bath and a 1 M solution of borane−THF in tetrahydrofuran (17 mL) was added dropwise in a reaction that was effervescent at the outset. The solution was stirred overnight at room temperature, re-cooled in an ice bath and water (17 mL) was added dropwise followed by solid sodium percarbonate (7.10 g, 68 mmol). The mixture was immersed in a 50 °C bath and stirred for 70 min to generate a solution. The two-phase system was cooled, then equilibrated with ethyl acetate/hexane (1:1) (170 mL). The organic layer was washed with water (2 × 25 mL) and brine (20 mL), dried and the solvents evaporated to leave the diol mixture as a colorless oil, 2.76 g, TLC (ethyl acetate/hexane, 1:1) R_f = 0.37 major, 0.30 minor. This material was passed through a short flash column using ethyl acetate/hexane (1:1) and silica gel G. The effluent, obtained after exhaustive elution, was evaporated, taken up in ethyl acetate, filtered and chromatographed on an HPLC column (see Exp. Sect.) using ethyl acetate/hexane (2:1) as mobile phase. Isomer **15** emerged at an effluent maximum of 2.9 L and was obtained as a colorless oil that very slowly and incompletely solidified, 1.3114 g; m.p. 68−69 °C. $[\alpha]_D$ = +45.2 (*c* = 0.58, methanol). ^{1}H NMR: δ = −0.002 (s, 3 H), 0.011 (s, 3 H), 0.89 (s, 9 H), 0.93 (s, 3 H), 1.17 (m, 1 H), 1.22 (s, 6 H), 1.25−1.6 (m, 16 H), 1.68 (m, 1 H), 1.80 (m, 2 H), 1.89 (m, 1 H), 3.66 (dd, *J* = 4.8 and 11 Hz, 1 H), 3.72 (dd, *J* = 3.3 and 11 Hz, 1 H), 4.00 (m, 1 H) ppm. LR-ES(−): *m*/*z* = 412 [M], 411 [M − H]. HR-ES(+): *m*/*z* calcd. for [M + Na]: 435.3265, found 435.3269.

Isomer **14** was eluted at an effluent maximum of 4.9 L, obtained as a crystalline residue, 0.8562 g, then recrystallized from ethyl acetate/hexane; m.p. 102−103°C. $[\alpha]_D$ = +25.2 (*c* = 0.49, methanol). ^{1}H NMR: δ = −0.005 (s, 3 H), 0.009 (s, 3 H), 0.89 (s, 9 H), 0.93 (s, 3 H), 1.16 (m, 1 H), 1.22 (s, 6 H), 1.3−1.5, (m, 14 H), 1.57 (m, 2 H), 1.67 (m, 1 H), 1.80 (m, 2 H), 1.91 (m, 1 H), 3.54 (dd, *J* = 4.8 and 11 Hz, 1 H), 3.72 (dd, *J* = 2.9 and 11 Hz, 1 H), 4.00 (m, 1 H) ppm. LR-ES(−): *m*/*z* = 412 [M], 411 [M − H]. $C_{24}H_{48}O_3Si$: calcd. C 69.84, H, 11.72; found C 69.91, H 11.76.

(*S*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-7-methyloctane-1,7-diol (17) and (*R*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-7-methyloctane-1,7-diol (16): A solution of the alkenediol mixture **13a** and **13b** (0.61 g) in ethyl acetate was stirred overnight in the presence of 1% Pt−C (197 mg) and under a hydrogen pressure of 1 atm. The catalyst was filtered off, the filtrate concentrated and chromatographed on an HPLC column (see Exp. Sect.) using ethyl acetate/hexane (2:1) as mobile phase. The (*S*) isomer **17** (0.32 g, colorless oil) emerged at an effluent maximum of 3400 mL: $[\alpha]_D^{22}$ = +91.2 (*c* = 0.48, methanol). ^{1}H NMR (400 MHz): δ = −0.005 and 0.008 (s, 3 H each, Me_2Si), 0.88 (s, 9 H, Me_3C−Si), 0.92 (s, 3 H, C7a-Me), 1.15 (m, 1 H), 1.22 (s, 6 H), 1.2−1.8 (m, 21 H), 1.95 (m, 1 H), 3.62 and 3.68 (m, 1 H each, hydroxymethyl), 4.00 (m, 1 H) ppm. LR-ES(+): *m*/*z* = 426 [M], 425 [M − H], 495 [M − CH_2OH], 353 [M − CH_2CMe_2OH]. HRMS-ES(+): *m*/*z* calcd. for $C_{25}H_{50}O_3Si$: 449.3421 [M + Na], found 449.3423.

The (*R*) isomer **16**, quantitatively separated from **17**, was eluted at an effluent maximum of 4100 mL (0.28 g) and obtained as a colorless oil that crystallized from ethyl acetate; m.p. 95−96 °C. $[\alpha]_D^{25}$ = +34.8 (*c* = 0.89, methanol). ^{1}H NMR: δ = −0.006 and 0.007 (s, 3 H each), 0.88 (s, 9 H), 0.92 (s, 3 H), 1.14 (m, 1 H), 1.21 (s, 6 H), 1.2−1.8 (m, 20 H), 1.81 (m, 1 H), 1.88 (m, 1 H), 3.63 and 3.69 (m, 1 H each), 4.00 (m, 1 H) ppm. LR-ES: *m*/*z* = 426 [M^+], 425 [M − H], 495 [M − CH_2OH], 353 [M − CH_2CMe_2OH]. HRMS-ES(+): *m*/*z* calcd. for $C_{25}H_{50}O_3Si$: 449.3421 [M + Na], found 449.3425.

(*S*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-7-hydroxy-7-methyloctanal (18): Pyridinium chlorochromate (790 mg, 3.66 mmol) was added in one portion to a stirred mixture containing the diol **17** (0.7369 g, 1.727 mmol), sodium acetate (0.46 g, 1.2 mmol), Celite (500 mg) and dichloromethane (12 mL). After 2.5 h, the mixture was diluted with cyclohexane (5 mL) and passed through a plug of silica gel G previously equilibrated with diethyl ether. Filtrate and diethyl ether were evaporated and the residue flash-chromatographed with ethyl acetate/hexane (1:3) as mobile phase affording the aldehyde **18** as a colorless oil, 0.61 g, 83%. ^{1}H NMR: δ = 0.000 and 0.012 (s, 3 H each), 0.89 (s, 9 H), 0.95 (s, 3 H), 1.14 (m, 1 H), 1.21 (s, 6 H), 1.2−2.0 (m, 19 H), 2.43 and 2.59 (m, 1 H each), 4.00 (m, 1 H), 9.77 (m, 1 H) ppm.

(*S*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2-methylnon-8-yn-2-ol (19a). (a) Synthesis from 18: Powdered potassium carbonate (0.34 g, 2.46 mmol) was added to a stirred, ice-cold mixture of the aldehyde **18** (0.61 g, 1.436 mmol), dimethyl 1-(1-diazo-2-oxopropyl)phosphonate (0.41 g, 2.13 mmol) and methanol (9 mL). The ice bath was removed after 1 h and stirring at room temperature continued for 5.5 h. The mixture was then diluted with hexane (30 mL) and water (20 mL), the aqueous phase was extracted once with hexane (30 mL), and once with diethyl ether (30 mL). All three extracts were combined, washed with water (3 × 10 mL), once with brine (10 mL), dried (sodium sulfate) and the solvents evaporated to give a colorless oily residue, 0.6 g, which was flash-chromatographed with ethyl acetate/hexane (1:9) as mobile phase affording **19a** as a colorless oil, 0.5552 g, 92%. $[\alpha]_D^{22}$ = +43.5 (*c* = 0.2, methanol). ^{1}H NMR: δ = −0.005 and 0.009 (s, 3 H each), 0.89 (s, 9 H), 0.90 (s, 3 H), 1.22 (s, 6 H), 1.2−1.6 (m, 16 H), 1.67 (m, 1 H), 1.79 (m, 2 H), 1.90 (m, 1 H), 1.92 (dd, *J* = 2.6 Hz, 1 H), 2.31 and 2.37 (m, 1 H each), 4.00 (m, 1 H) ppm. LR-EI(+): *m*/*z* = 420 [M], 405 [M − Me], 363 [M − C_4H_9]. HRMS-EI(+): *m*/*z* calcd. for $C_{26}H_{48}O_2Si$: 420.3424 [M], found 420.3433.

(b) Synthesis from 22: Lithium acetylide DMA complex (0.110 g, 1.19 mmol) was added to a solution of **22** (0.2018 g (0.386 mmol) in dimethyl sulfoxide (1.5 mL) and tetrahydrofuran (0.15 mL). The mixture was stirred overnight. TLC (ethyl acetate/hexane, 1:4) showed a mixture of two spots traveling very close together (R_f = 0.52 and 0.46). Flash-chromatography using ethyl acetate/hexane (1:19) as mobile phase separated this mixture only partially. Nevertheless fractions at the beginning of the eluted band contained pure **12**, which is the elimination product of **22**, and was produced as the major product. Fractions at the end of the elution band, however, were also homogeneous and gave the desired acetylene upon evaporation. The elution was monitored by TLC (methanol/dichloromethane, 1:19). The NMR spectrum of this product was identical with **19a** prepared from **18** as described above.

(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyl-1-[(*S*)-5-methyl-1-prop-2-ynyl-5-trimethylsilanyloxyhexyl)octahydroindene (19b): A mixture of the acetylene **19a** (0.517 g, 1.23 mmol), cyclohexane (8 mL), and 1-(trimethylsilyl)imidazole (0.29 mL, 2 mmol) exhibited no residual **19a** after 4 h (TLC, ethyl acetate/hexane, 1:9). The mixture was applied to a silica gel G plug that was eluted with hexane to give **19b** as a colorless syrup, 0.5638 g, 93%. ^{1}H NMR: δ = −0.005 and 0.008 (s, 3 H each, Me_2Si), 0.10 (s, 9 H), 0.89 (s, 9 H), 0.91 (s, 3 H), 1.20 (s, 6 H), 1.2−1.63 (m, 14 H), 1.66 (m, 1 H), 1.74−1.84 (m, 2 H), 1.90 (m, 1 H), 1.91 (dd, *J* = 2.6 Hz, 1 H), 2.30 and 2.37 (m, 1 H each), 4.00 (m, 1 H) ppm. LR-FAB(+): *m*/*z* = 492 [M], 401 [M − H], 477 [M − Me], 435 [M − C_4H_9], 403 [M − OTMS].

(*S*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-1,1,1-trifluoro-10-methyl-2-(trifluoromethyl)undec-3-yne-2,10-diol (20b): The acetylene **19b** was converted into **20b** via **20a** as described for **25b**. Diol **20b**, however, was obtained in crystalline form from dichloromethane, m.p. 131 °C. ^{1}H NMR: δ = 0.94 (s, 3 H), 1.23 (m, 1 H), 1.25 (s, 6 H), 1.25−1.85 (m, 10 H), 1.88 (m, 1 H), 2.32 (dd, J_{gem} = 16.9, *J* = 6.6 Hz, 1 H), 2.55 (dd, J_{gem} = 17.2, *J* = 4 Hz, 1 H), 4.09 (m, 1 H) ppm. $[\alpha]_D^{25}$ = +16.2 (*c* = 0.44, methanol). LR-APCI(+): *m*/*z* = 472 [M], 471 [M − H]. HRMS-ES(−): *m*/*z* calcd. for $C_{23}H_{34}F_6O_3$: 471.2339 [M − H], found 471.2345. $C_{23}H_{34}F_6O_3$: calcd. C 58.46, H 7.25, found C 58.42, H 7.39.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-4-one (21a): Pyridinium dichromate (1.16 g, 3.08 mmol) was added to a stirred suspension of **20b** (0.3326 g, 0.704 mmol), Celite (0.6 g), and dichloromethane (12 mL). After 6 h the mixture was diluted with diethyl ether (15 mL) and charged to a silica gel plug (2.4 g) that was exhaustively eluted with diethyl ether. The combined diethyl ether effluent was evaporated and the residue crystallized from ethyl acetate/hexane, 0.292 g (88%), then recrystallized from the same solvent to give needles, m.p. 139−140 °C; the crystal analysis is based on a crystal 0.35 × 0.07 × 0.05 mm, $C_{23}H_{32}F_3O_3$, orthorhombic, space group $P2_12_12_1$ with unit cell dimensions *a* = 8.5350(5), *b* = 14.6309(9), *c* = 18.7254(11) Å, cell volume 2338.3(2) Å^3 (*Z* = 4), $d_{calcd.}$ = 1.336 g·cm^{-3}. Analysis was based on 20415 reflections collected and 4782 [*R*(int) = 0.0589] independent reflections, 123(1) K, wavelength 0.71073 Å, absorption coefficient 0.118 mm^{-1}, *F*(000) = 992, Theta range for data collection 1.77 to 26.37°, data/restraints/parameters 4782/0/300. The structure was refined by full-matrix least-squares on F^2. Final *R* indices [$I > 2\sigma(I)$] were *R*1 = 0.0417 and *wR*2 = 0.1103 and *R* indices (all data) *R*1 = 0.0480 and *wR*2 = 0.1136, absolute structure parameter −0.3(5), largest diff. peak and hole 0.231 and −0.287 e·Å^{-3}. $[\alpha]_D^{25}$ = −5.5 (*c* = 0.45, methanol). ^{1}H NMR: δ = 0.64 (s, 3 H), 1.25 (s, 6 H), 1.3−2.44 (m, 21 H), 2.48 (dd, J_{gem} = 11, *J* = 7.3 Hz, 1 H), 2.57 (dd, J_{gem} = 17.6, *J* = 4 Hz, 1 H) ppm. LR-APCI(+): *m*/*z* = 470 [M], 469 [M − H]. HRMS-ES(−): *m*/*z* calcd. for $C_{23}H_{32}F_6O_3$: 469.2183 [M − H], found 469.2189. $C_{23}H_{34}F_6O_3$: calcd. C 58.71, H 6.86, found C 58.77, H 6.74.

CCDC-231751 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-1-(4-methyl-4-trimethylsilanyloxypentyl)-5-(trifluoromethyl)-5-trimethylsilanyloxyhex-3-ynyl]octahydroinden-4-one (21b): A mixture of the ketone **21a** (0.3184 g, 0.677 mmol), diethyl ether (3 mL), and 1-(trimethylsilyl)imidazole 0.30 mL, 2.04 mmol) was agitated for 1 h. The disappearance of starting material and generation of **21b** was demonstrated by TLC (ethyl acetate/hexane, 1:39 and methanol/dichloromethane, 1:19). The residue obtained after evaporation of solvent was flash-chromatographed with a stepwise gradient of ethyl acetate/hexane (1:39 to 1:19) as mobile phase to furnish **21b** as a colorless residue, 0.30 g. ^{1}H NMR: δ = 0.10 (s, 9 H), 0.28 (s, 9 H), 0.64 (s, 3 H), 1.20 (s, 6 H), 1.2−1.6 (m, 10 H), 1.66−1.82 (m, 3 H), 1.82−1.98 (m, 2 H), 1.98−2.08 (m, 2 H), 2.2−2.34 (m, 2 H), 2.45−2.52 (m, 2 H) ppm. LRMS-ES(+): *m*/*z* = 541 [M − TMS], 525 [M − OTMS]. HRMS-ES(+): *m*/*z* = calcd. for $C_{29}H_{48}F_6O_3Si_2$: 637.2938 [M + Na], found 637.2941.

(*R*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-7-iodo-2-methylheptan-2-ol (22): A stirred mixture of triphenylphosphane (0.333 g, 1.27 mmol) and imidazole (0.255 g, 3 mmol) in dichloromethane (3 mL) was cooled in an ice bath and iodine (0.305 g, 1.20 mmol) was added. This mixture was stirred for 10 min then a solution of **15** (0.4537 g, 1.10 mmol) in dichloromethane (3 mL) was added dropwise over a 10 min period. The mixture was stirred in the ice bath for 30 min then at ambient temperature for 2 $^3/_4$ h. TLC (ethyl acetate/hexane, 1:1) confirmed the absence of starting material. A solution of sodium thiosulfate (0.1 g) in water (5 mL) was added, the mixture equilibrated and the organic phase washed with 0.1 N sulfuric acid (10 mL) containing a few drops of brine then with water/brine (1:1, 2 × 10 mL), once with brine (10 mL) then dried and the solvents evaporated. The residue was purified by flash chromatography using ethyl acetate/hexane (1:9) as mobile phase to furnish **22** as a colorless syrup, 0.5637 g, 98%. ^{1}H NMR: δ = −0.005 (s, 3 H), 0.010 (s, 3 H), 0.89 (s, 9 H), 0.92 (s, 3 H), 1.23 (s, 6 H), 1.1−1.6 (m, 16 H), 1.68 (m, 1 H), 1.79 (m, 2 H), 1.84 (m, 1 H), 3.37(dd, *J* = 4 and 10 Hz, 1 H), 3.47 (dd, *J* = 3 and 10 Hz, 1 H), 4.00 (m, 1 H) ppm. LR-EI(+): *m*/*z* = 522 [M], 465 [M − C_4H_9], 477 [M − C_4H_9 − H_2O]. HR-EI(+): *m*/*z* calcd. for $C_{24}H_{47}IO_2Si$: 522.2390, found 522.2394.

(*S*)-3-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-7-hydroxy-7-methyloctanal (23): The diol **16** was converted into **23** as described for the synthesis of **18** and obtained as a colorless oil. ^{1}H NMR: δ = 0.000 and 0.016 (s, 3 H each), 0.89 (s, 9 H), 0.96 (s, 3 H), 1.16 (m, 1 H), 1.21 (s, 6 H), 1.2−2.1 (m, 19 H), 2.33 and 2.42 (m, 1 H each), 4.00 (m, 1 H), 9.78 (m, 1 H) ppm.

(*R*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2-methylnon-8-yn-2-ol (24a): The aldehyde **23** was converted into **24a** as described for the preparation of **19a** and obtained as a colorless oil: $[\alpha]_D^{22}$ = +29.0 (*c* = 0.51, methanol). ^{1}H NMR: δ = −0.006 and 0.007 (s, 3 H each), 0.89 (s, 9 H), 0.92 (s, 3 H), 1.17 (m, 1 H), 1.22 (s, 6 H), 1.2−1.7 (m, 17 H), 1.74−1.88 (m, 2 H), 1.90 (dd, *J* = 2.6 Hz, 1 H), 2.14 (ddd, J_{gem} = 16.8, *J* = 6, *J* = 2.4 Hz, 1 H), 2.33 (ddd, J_{gem} = 17.2, *J* = 3.6, *J* = 3.2 Hz, 1 H), 4.00 (m, 1 H) ppm. LR-EI(+): *m*/*z* = 420 [M], 405 [M − Me], 363 [M − C_4H_9].

(1*R*,*3aR*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyl-1-[(*R*)-5-methyl-1-prop-2-ynyl-5-trimethylsilanyloxyhexyl)octahydroindene (24b): The acetylene **24a** was converted into **24b** as described for the preparation of **19b** and obtained as a colorless oil. $[\alpha]_D^{22}$ = +29.0 (*c* = 0.51, methanol). ^{1}H NMR: δ = −0.006 and 0.007 (s, 3 H each), 0.10 (s, 9 H), 0.89 (s, 9 H), 0.92 (s, 3 H), 1.18 (m, 1 H), 1.20 (s, 6 H), 1.2−1.63 (m, 14 H), 1.66 (m, 1 H), 1.74−1.87 (m, 2 H), 1.89 (dd, *J* = 2.6 Hz, 1 H), 1.93 (m, 1 H), 2.13 (ddd, J_{gem} = 16.9, *J* = 6, *J* = 2.4 Hz, 1 H), 2.33 (ddd, J_{gem} = 17.2, *J* = 3.3, *J* = 3.1 Hz, 1 H), 3.99 (m, 1 H) ppm. LR-EI(+): *m*/*z* = 420 [M], 405 [M − Me], 363 [M − C_4H_9].

(*R*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-1,1,1-trifluoro-10-methyl-2-(trifluoromethyl)undec-3-yne-2,10-diol (25b): A solution of the acetylene **24b** (0.5746 g, 1.166 mmol) in tetrahydrofuran (5 mL) was cooled in a dry-ice bath, then a 1.6 M solution of butyllithium in hexane (1.0 mL) was added dropwise over an 8 min period. To this solution was added hexafluoroacetone (ca. 0.5 mL), previously condensed in a dry-ice-filled trap. Already after 5 min starting material was no longer detectable (TLC, 1:9 ethyl acetate hexane, **25a** had R_f = 0.7). To the mixture was added dropwise pH 7 phosphate buffer (5 mL) and extracted with 40 and 20 mL of hexane. The combined extracts were washed with brine (10 mL), dried (sodium sulfate) and the solvents evaporated to give crude **25a** as a colorless oil (0.90 g). This material was dissolved in acetonitrile (10 mL), the solution was cooled in an ice bath and fluorosilicic acid solution[23] (2.20 mL) was added. After 4 h of stirring the desilylation was complete (TLC, ethyl acetate/hexane, 1:4 and methanol/dichloromethane, 1:19). The mixture was diluted with ethyl acetate (40 mL), water (15 mL) was added and the aqueous phase extracted with water (2 × 15 mL) and with brine (15 mL). The combined extracts were dried (sodium sulfate) and the solvents evaporated. The resulting oil was flash chromatographed to furnish **25b** as a sticky residue that could be converted into a white foam from dichloromethane, 0.5280 g. $[\alpha]_D^{22}$ = +6.06 (*c* = 0.33, methanol). ^{1}H NMR: δ = 0.95 (s, 3 H), 1.19 (m, 1 H), 1.25 (s, 6 H), 1.25−1.91 (m, 10 H), 1.96 (m, 1 H), 2.17 (dd, J_{gem} = 17.2, *J* = 7 Hz, 1 H), 2.46 (dd, J_{gem} = 17.2, *J* = 3.7 Hz, 1 H), 4.09 (m, 1 H) ppm. LR-APCI(+): *m*/*z* = 472 [M], 471 [M − H]. HRMS-ES(−): *m*/*z* calcd. for $C_{23}H_{34}F_6O_3$: 471.2339 [M − H], found 471.2344.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-4-one (26a): The triol **25b** was oxidized to **26a** and crystallized as described for the preparation of **21a**; m.p. 159 °C. $[\alpha]_D^{22}$ = −17.4 (*c* = 0.34, methanol). ^{1}H NMR: δ = 0.66 (s, 3 H), 1.26 (s, 6 H), 1.25−2.4 (m, 18 H), 2.16−2.31 (m, 3 H) 2.44−2.53 (m, 2 H) ppm. LR-APCI(+): *m*/*z* = 470 [M], 469 [M − H]. HRMS-ES (−): *m*/*z* calcd. for $C_{23}H_{32}F_6O_3$: 469.2183 [M − H], found 469.2186. $C_{23}H_{34}F_6O_3$: calcd. C 58.71, H 6.86; found C 58.75, H 6.91.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-1-(4-methyl-4-trimethylsilanyloxypentyl)-5-(trifluoromethyl)-5-trimethylsilanyloxyhex-3-ynyl]octahydroinden-4-one (26b) and (1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(4-methyl-4-trimethylsilanyloxypentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-4-one (26c): A mixture of the ketone **26a** (0.4116 g, 0.8748 mmol), diethyl ether (4 mL), and 1-(trimethylsilyl)imidazole) (0.40 mL, 2.73 mmol) was agitated for 15 h. The solution was evaporated and the residue flash-chromatographed with ethyl acetate/hexane (1:39 and 1:4) as mobile phase. The first solvent eluted **26b**, the second **26c**. Although the mixture of these two compounds was used in the next step, the two components were separated for analysis. Thus, the disilyl ether **26b** was obtained as a colorless oil, 0.3751 g. ^{1}H NMR (400 MHz): δ = 0.00 (s, 9 H), 0.18 (s, 9 H), 0.56 (s, 3 H), 1.11 (s, 6 H), 1.1−1.9 (m, 17 H), 1.96 (m, 1 H), 2.16 (m, 2 H), 2.36 (m, 1 H) ppm. LR-ES(+): *m*/*z* = 655 [M − TMS + TFA − H], 541 [M − TMS]. Compound **26c** was also obtained as an oil, 0.1234 g. ^{1}H NMR: δ = 0.00 (s, 9 H), 0.54 (s, H), 1.11 (s, 6 H), 1.1−2.0 (m, 7 H), 2.1−2.2 (m, 2 H), 2.3−2.4 (m, 1 H) ppm. LR-ES(+): *m*/*z* = 655 [M + TFA − H], 541 [M − H].

(1*R*,3*S*)-5-{2-[(1*R*,3a*S*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-(4*E*)-ylidene]ethylidene}-4-methylenecyclohexane-1,3-diol (6a): A stirred solution of **27a** (0.2528 g, 0.434 mmol) in tetrahydrofuran (2 mL) was cooled to −75 °C and a 1.6 M solution of butyllithium in hexane (0.28 mL, 44 mmol) was added dropwise to generate a deep-red ylide solution. After 10 min, a solution of **21b** in tetrahydrofuran (2 mL) was added during a period of 20 min. The reaction was quenched after 4.5 h by the addition of pH 7 phosphate buffer (4 mL). The mixture was warmed to room temperature then extracted with hexane (35 mL). The hexane layer was washed with brine (5 mL), dried (sodium sulfate) and the solvents evaporated to give a colorless oil that was flash-chromatographed with ethyl acetate/hexane (1:79 and 1:39) as

mobile phase. The mixture of the tetra- and trisilyl ethers **28a** was eluted using the latter solvent, obtained as a colorless, honey-like syrup (0.197 g) wherein the trisilyl ether predominated, then dissolved in a 1 M solution of tetrabutylammonium fluoride (3 mL). The deprotection was monitored by TLC using ethyl acetate as solvent. After 24 h the mixture was diluted with brine (5 mL), stirred for 5 min then distributed between ethyl acetate (35 mL and water (8 mL). The organic layer was washed with water (5 × 10 mL), brine (5 mL), and dried (sodium sulfate). The resulting residue was flash-chromatographed with ethyl acetate/hexane (2:3 and 2:1) as mobile phase. The latter solvent eluted the product. The residue was taken up in methyl formate, filtered and the solvents evaporated to provide **6a** as a foam, 0.1134 g, 78% total yield for condensation and deprotection: $[\alpha]_D = +11.1$ ($c = 0.31$, methanol). UV (methanol): $\lambda_{max.}$ (ε) = 212 (16247), 264 (18315) nm. ^{1}H NMR: $\delta = 0.55$ (s, 3 H, C7a-Me), 1.25 (s, 6 H), 1.2−1.8 (m, 18 H), 1.90 (m, 3 H), 2.02 (m, 2 H), 2.16 (m, 1 H), 2.33 (m, 2 H), 2.58 (m, 2 H), 2.83 (m, 1 H), 4.24 (m, 1 H), 4.43 (m, 1 H), 5.00 and 5.33 (s, 2 H each), 6.02 (d, $J = 11.4$ Hz, 1 H), 6.37 (d, $J = 11.4$ Hz, 1 H) ppm. ^{19}F NMR (376 MHz): $\delta = -76.63$ and −76.67 (2q, 6 F, overlapping) ppm. LR-ES(+): *m*/*z* = 719 [M + TFA − H], 607 [M + H], 606 [M], 605 [M − H]. HRMS-ES(+): *m*/*z* calcd. for $C_{32}H_{44}F_6O_3$: 629.3036 [M + Na], found 629.3039.

(1*R*,3*R*)-5-{2-[(1*R*,3a*S*,7a*R*)-7a-Methyl-1-[(*S*)-6,6,6-trifluoro-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-(4*E*)-ylidene]ethylidene}-cyclohexane-1,3-diol (6b): According to the procedure given above for the preparation of **6a**, reagent **27b** (2685 mg, 0.470 mmol) in tetrahydrofuran (2 mL) was deprotonated with a 1.6 M solution of butyllithium in hexane (0.30 mL) at −75 °C then allowed to reacted with the ketone **21b** (0.1428 g, 0.232 mmol) in tetrahydrofuran (2 mL) to furnish the mixture of the tetra- and tri-silyl ethers **28b** and purified by flash chromatography (0.2141 g). This material was deprotected in a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (2 mL) within 48 h and purified by flash chromatography (2:3 and 2:1 ethyl acetat/hexane) to give a residue that was dissolved in methyl formate (5 mL), filtered and the solvents evaporated to furnish **6b** as a foam, 0.1204 g, 87%. $[\alpha]_D = +42.9$ ($c = 0.35$, methanol). UV: $\lambda_{max.}$ (ε) = 242 (34077), 251 (40515), 260 (27531), 234 (sh, 22354), 223 (sh, 13098) nm. ^{1}H NMR: $\delta = 0.55$ (s, 3 H), 1.25 (s, 6 H), 1.2−2.1 (m, 22 H), 2.23 (m, 2 H), 2.35 (m, 2 H), 2.48 (m, 1 H), 2.56 (m, 2 H), 2.77 (m, 2 H), 4.05 (m, 1 H), 4.09 (m, 1 H), 5.86 (d, $J = 11$ Hz, 1 H), 6.31 (d, $J = 11$ Hz, 1 H) ppm. ^{19}F NMR (376 MHz): $\delta = -76.63$ and −76.64 (2q, 6 F, overlapping) ppm. LR-APCI(+): *m*/*z* = 577 [M − OH], 559 [M − OH − H_2O]. HRMS-ES(+): *m*/*z* calcd. for $C_{31}H_{44}F_6O_4$: 617.6588 [M + Na], found 617.6590.

(1*R*,3*S*)-5-{2-[(1*R*,3a*S*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-(4*E*)-ylidene]ethylidene}-4-methylenecyclohexane-1,3-diol (7a): According to the procedure given above for the preparation of **6a**, reagent **27a** (0.2333 g, 0.400 mmol) in tetrahydrofuran (2 mL) was deprotonated with a 1.6 M solution of butyllithium in hexane (0.25 mL) at −75 °C then allowed to react with a 3:1 mixture of the ketones **26b** and **26c** (0.1295 g, 0.2166 mmol) in tetrahydrofuran (2 mL) to furnish the mixture of the tetra- and tri-silyl ethers **29a**, which were purified by flash chromatography using ethyl acetate/hexane (1:79) to elute **29a** (R^3 = TMS) and ethyl acetate/hexane (1:39) as mobile phase to elute **29a** (R^3 = H). Both products were deprotected in a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (3 mL) within 27 h and purified by flash chromatography (ethyl acetate/hexane, 2:3 and 2:1) to give a residue that was dissolved in methyl formate (5 mL), filtered and the solvents evaporated to yield **7a** as a foam, 0.1035 g, 79% total yield for both condensation and deprotection. $[\alpha]_D = +15.0$ ($c = 0.39$, methanol). UV: $\lambda_{max.}$ (ε) = 215 (14953), 265 nm (17848). ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.52$ (s, 3 H, C7a-Me), 1.05 (s, 6 H), 1.1−1.5 (m, 16 H), 1.79 (m, 2 H), 1.94 (m, 2 H), 2.2−2.5 (m, 5 H), 2.80 (m, 1 H), 3.98 (br. s, 1 H), 4.07 (br. s, 1 H), 4.19 (br. s, 1 H), 4.55 (br. s, 1 H), 4.75 and 5.22 (br. s, 1 H each) 5.99 (d, $J = 10.7$ Hz, 1 H), 6.20 (d, $J = 10.7$ Hz, 1 H), 8.94 (s, 1 H) ppm. ^{19}F NMR (376 MHz): $\delta = -76.74$ (s, 6 F) ppm. LR-ES(+): *m*/*z* = 719 [M + TFA − H], 605 [M − H]. HRMS-ES(+): *m*/*z* calcd. for $C_{32}H_{44}F_6O_4$: 629.3036 [M + Na], found 629.3035.

(1*R*,3*R*)-5-{2-[(1*R*,3a*S*,7a*R*)-7a-Methyl-1-[(*R*)-6,6,6-trifluoro-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-(trifluoromethyl)hex-3-ynyl]octahydroinden-(4*E*)-ylidene]ethylidene}-cyclohexane-1,3-diol (7b): According to the procedure given above for the preparation of **6a**, reagent **27b** (0.2730 g, 0.478 mmol) in tetrahydrofuran (2 mL) was deprotonated with a 1.6 M solution of butyllithium in hexane (030 mL) at −75 °C then allowed to react with a 3:1 mixture of the ketones **26b** and **26c** (0.1227 g, 0.2056 mmol) in tetrahydrofuran (2 mL) to furnish the mixture of the tetra- and trisilyl ethers **29b** which were purified by flash chromatography using 1:39 ethyl acetate/hexane to elute **29b** (R^3 = TMS) and **29b** (R^3 = H) as a mixture. This mixture was deprotected in a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (3 mL) within 48 h and purified by flash chromatography (ethyl acetate/hexane, 2:3 and 2:1) to give a residue that was dissolved in methyl formate (5 mL), filtered and the solvents evaporated to yield **7b** as a foam, 0.0934 g, 76% total yield for both condensation and deprotection. $[\alpha]_D = +43.8$ ($c = 0.38$, methanol). UV: $\lambda_{max.}$ (ε) = 242 (34229), 251 (40595), 260 (27657), 226 (sh, 13529), 234 nm (sh, 22676). ^{1}H NMR ([D$_6$]DMSO): $\delta = 0.52$ (s, 3 H), 1.05 (s, 6 H), 1.1−1.7 (m, 19 H), 1.7−2.1 (m, 5 H), 2.28 (m, 2 H), 2.42 (s, 1 H), 2.45 (m, 2 H), 2.75 (m, 1 H), 3.80 (br. s, 1 H), 3.87 (br.s, 1 H), 5.81 (d $J = 11.7$ Hz, 1 H), 6.08 (d, $J = 11.7$ Hz, 1 H), 8.42 (s, 1 H) ppm. ^{19}F NMR (376 MHz): $\delta = -76.75$ (s, 6 F) ppm. LR-APCI(+): *m*/*z* = 577 [M − OH], 559 [M − H_2O]. HRMS-ES(+): *m*/*z* calcd. for $C_{31}H_{44}F_6O_4$: 617.6588 [M + Na], found 617.6586.

5-[2-(4-Hydroxy-4-methylpentyl)-4,4-dimethyl-1,3-dioxolan-2-yl]-2-methylpentan-2-ol (31): A solution of the diester **30** (3.02 g, 10 mmol) in tetrahydrofuran (90 g) was cooled in an ice bath and a 3 M solution of methylmagnesium bromide in diethyl ether was added at an internal temperature below 10 °C. The mixture was stirred at room temperature for 1.5 h, then re-immersed in the ice bath and saturated ammonium chloride (25 mL) was added dropwise below 25 °C. The resulting mixture was equilibrated with water (25 mL), ethyl acetate (100 mL) and a small amount of 2 N hydrochloric acid to generate a clear aqueous layer. The aqueous layer was re-extracted with ethyl acetate (3 × 50 mL) and the organic layers combined and washed with 1:1 brine/water (25 mL) and brine (10 mL) then dried and the solvents evaporated to leave an oily residue that was purified by flash chromatography using ethyl acetate/hexane (1:1) and ethyl acetate as mobile phase to afford **31** as a colorless oil, 2.60 g, 95%. ^{1}H NMR (300 MHz): $\delta =$ 1.21 (s, 12 H), 1.47 (m, 8 H), 1.64 (m, 4 H), 3.97 (s, 4 H) ppm. LR-MS (+)LSIM *m*/*z* = 292 [M + NH_4], 274 [M], 257 [M − OH], 239 [M − OH − H_2O], 213 [M − OH − H_2O − C_2H_4O]. $C_{15}H_{30}O_4$: calcd. C 65.66, H 11.02; found C 65.27, H 10.96.

2,10-Dihydroxy-2,10-dimethylundecan-6-one (32a): A solution of **31** (2.60 g, 9.48 mmol) in tetrahydrofuran was cooled in an ice bath and 2 N hydrochloric acid was added. The solution was allowed to remain at room temperature for 21 h then sodium hydrogen car-

bonate (4 g) was added in portions whilst stirring. Ethyl acetate (50 mL) was added and the aqueous layer extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine (20 mL) then dried (sodium sulfate) and the solvents evaporated to give crude **32a** as a colorless oil (2.13 g). A small portion was purified by flash chromatography (ethyl acetate/hexane, 1:1). ^{1}H NMR (300 MHz): δ = 1.20 (m, 12 H), 1.43 (m, 4 H), 1.65 (m, 4 H), 2.43 (t, *J* = 7 Hz, 4 H) ppm.

2,10-Dimethyl-2,10-bis(trimethylsilanyloxy)undecan-6-one (32b): 1-(Trimethylsilyl)imidazole (2 mL, 13.6 mmol) was added to a solution of **32a** (1.10 g) in dichloromethane (20 mL). The colorless mixture was allowed to remain at room temperature overnight then diluted with water (10 mL), stirred for 10 min and further admixed with dichloromethane (40 mL). The aqueous layer was re-extracted with dichloromethane (10 mL) and the combined extracts were washed with water (50 mL) then dried (sodium sulfate) and the solvents evaporated to leave a **32b** as a colorless oil (1.74 g) that was flash chromatographed (ethyl acetate/hexane, 1:19). LR(+) LSIMS: *m*/*z* = 375 [M + H], 285 [M − OTMS].

(1*S*,5*R*)-1,5-Bis(*tert*-butyldimethylsilanyloxy)-2-methylene-3-{7-methyl-3-[4-methyl-4-(trimethylsilanyloxy)pentyl]-7-(trimethylsilanyloxy)oct-2-en-(*Z*)-ylidene}cyclohexane (33): According to the procedure given for the preparation of **6a**, reagent **27a** (0.609 g, 1.04 mmol) in tetrahydrofuran (20 mL) was deprotonated with a 1.6 M solution of butyllithium in hexane (0.6 mL) then allowed to react with **32b** (0.375 g, 1 mmol) in tetrahydrofuran (3.5 mL) to furnish **33** which was purified by flash chromatography using ethyl acetate/hexane (1:19) as mobile phase to yield pure **33** as a colorless oil, 0.38 g, 51.4%. ^{1}H NMR (300 MHz): δ = 0.06−0.10 (m, 30 H), 0.87 and 0.88 (s, 9 H each), 1.20 (s, 12 H), 1.44 (m, 14 H), 1.82 (m, 2 H), 2.13 (m, 2 H), 2.20 (m, 1 H), 2.42 (m, 1 H), 4.18 (m, 1 H), 4.39 (m, 1 H), 4.88 and 5.21 (s, 1 H each), 6.14 (s, 2 H) ppm.

(1*R*,3*S*)-5-[7-Hydroxy-3-(4-hydroxy-4-methylpentyl)-7-methyloct-2-en-(*Z*)-ylidene]-4-methylenecyclohexane-1,3-diol (5): Compound **33** obtained above was dissolved in tetrahydrofuran (2 mL), a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (5 mL) was added and kept at room temperature for 24 h, then water (10 mL) and ethyl acetate (75 mL) were added. The aqueous phase was re-extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with water (20 mL) and brine (25 mL), dried (sodium sulfate) and the solvents evaporated. The residue was flash-chromatographed (ethyl acetate/hexane, 1:1) to give **5** as colorless foam, 154 mg. $[\alpha]_D$ = +24.5 (*c* = 0.6, ethanol). ^{1}H NMR (300 MHz): δ = 1.21 (s, 12 H), 1.4−1.6 (m, 14 H), 1.98 (m, 2 H), 2.08 (m, 2 H), 2.31 (m, 1 H), 2.61 (m, 1 H), 4.22 (m, 1 H), 4.43 (m, 1 H), 4.99 and 5.33 (s, 1 H each), 6.16 (d, *J* = 11.5 Hz, 1 H), 6.27 (d, *J* = 11.5 Hz, 1 H). LR(+) LSIMS: *m*/*z* = 473 [M + TGLY], 366 [M], 349 [M − OH], 331 [M − OH − H_2O], 313 [M − OH − 2H_2O]. HR-FAB *m*/*z* calcd. for $C_{22}H_{38}O_4$: 389.2660 [M + Na], found 389.2668. $C_{22}H_{38}O_4$: calcd. C 72.09, H 10.45; found C 71.67, H 10.54.

Acknowledgments

We are grateful to Mr. Vance Bell for mass spectra, Mr. Gino Sasso for NMR spectra and Prof. Christopher Frampton for a crystal structure analysis.

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Received November 11, 2003

